Human Influenza in the US and NC: The Current Picture

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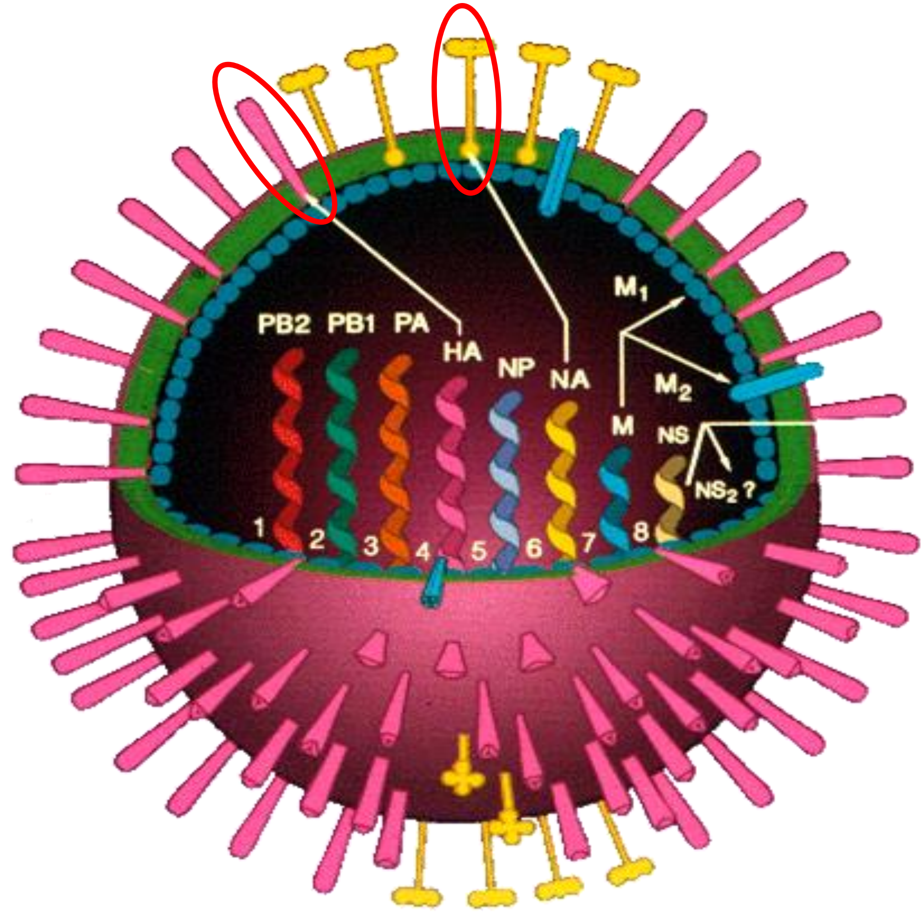
Outline

I. Biology of Influenza
   a. Basic virology/genetics
   b. Current zoonotic threats
   c. Transmission, treatment and prevention

II. Epidemiology of Influenza
   a. Surveillance for influenza in humans
   b. Current season picture

Flu Background

- Type A
  - Animals and humans
  - Epidemics, pandemics
- Type B
  - Humans
  - Epidemics
- Type C
  - Mild illness; no epidemics or pandemics



Hemagglutinin (HA) and Neuraminidase (NA) Function

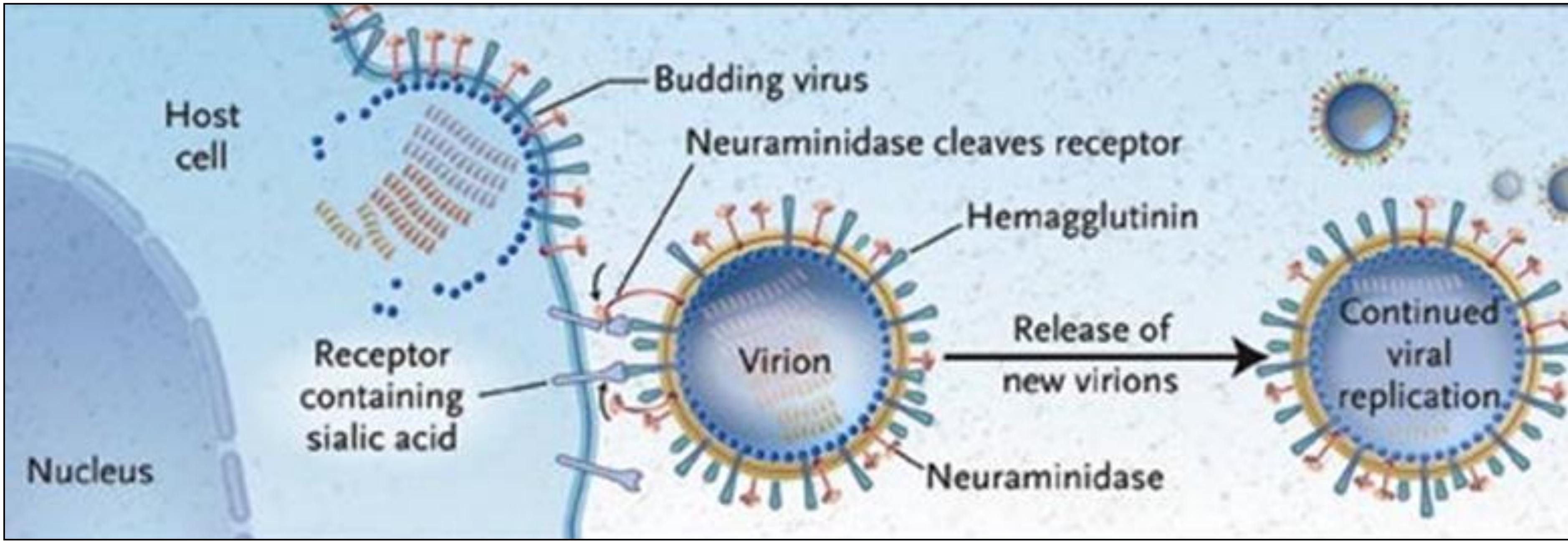
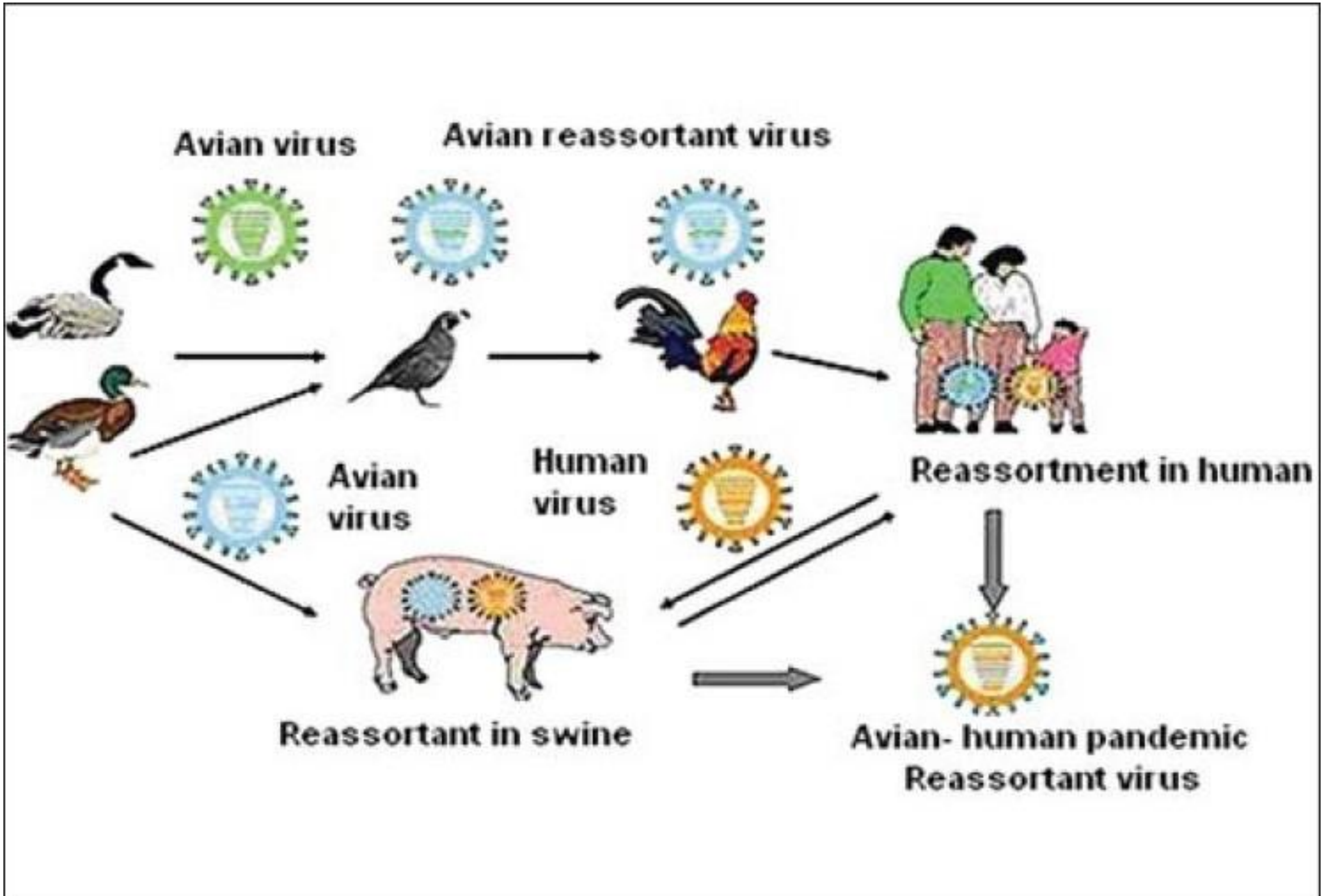


Image: Moscona A, New Engl J Med 2005. 353:1363-1373

Genetic Changes in Flu

- Antigenic **DRIFT**
  - Continual development of new strains through genetic mutations in HA and NA
  - A viruses >> B viruses
  - Seasonal epidemics
- Antigenic **SHIFT**
  - Human infection with new* HA or HA & NA
  - Influenza A only
  - Associated with pandemics

Generation of Novel Flu Strains



CDC, Emerging Infectious Disease Journal 2006;12(1)

Hemagglutinin

SubType	People	Poultry	Pigs	Bats / Other
H1				
H2				
H3				Other Animals
H4				Other Animals
H5				
H6				
H7				Other Animals
H8				
H9				
H10				
H11				
H12				
H13				
H14				
H15				
H16				
H17				
H18				

Neuraminidase

SubType	People	Poultry	Pigs	Bats / Other
N1				
N2				
N3				
N4				
N5				
N6				
N7				Other Animals
N8				Other Animals
N9				
N10				
N11				

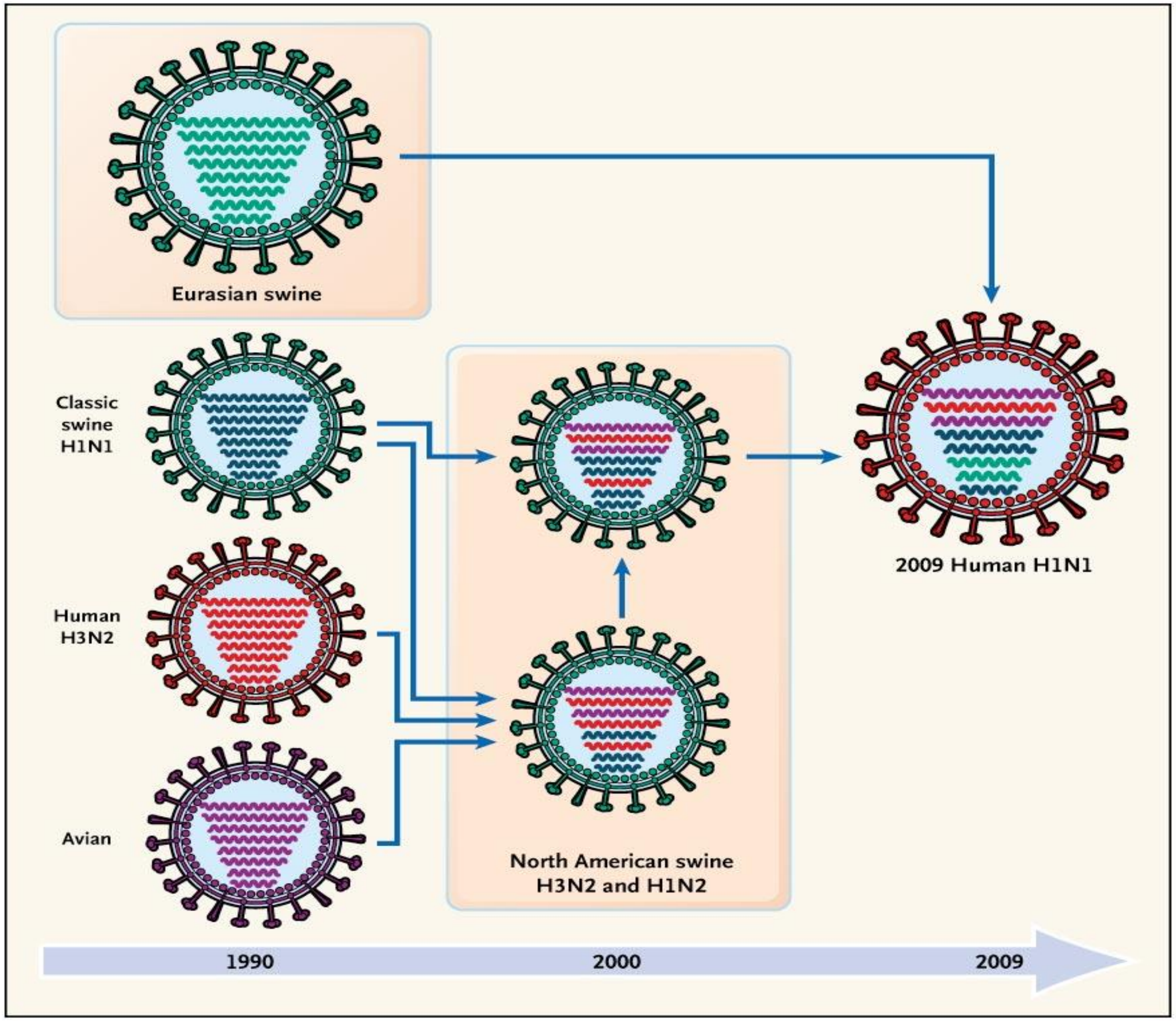
http://www.cdc.gov/flu/about/viruses/transmission.htm

Pandemic Influenza

Three Conditions:

1. New (“novel”) virus; all or most susceptible
2. Transmissible from person to person
3. Wide geographic spread

Reassortment Example: 2009 H1N1 Virus



Trifonov V et al. N Engl J Med 2009

Current Zoonotic Threats

H5N1
H7N9

H3N2v

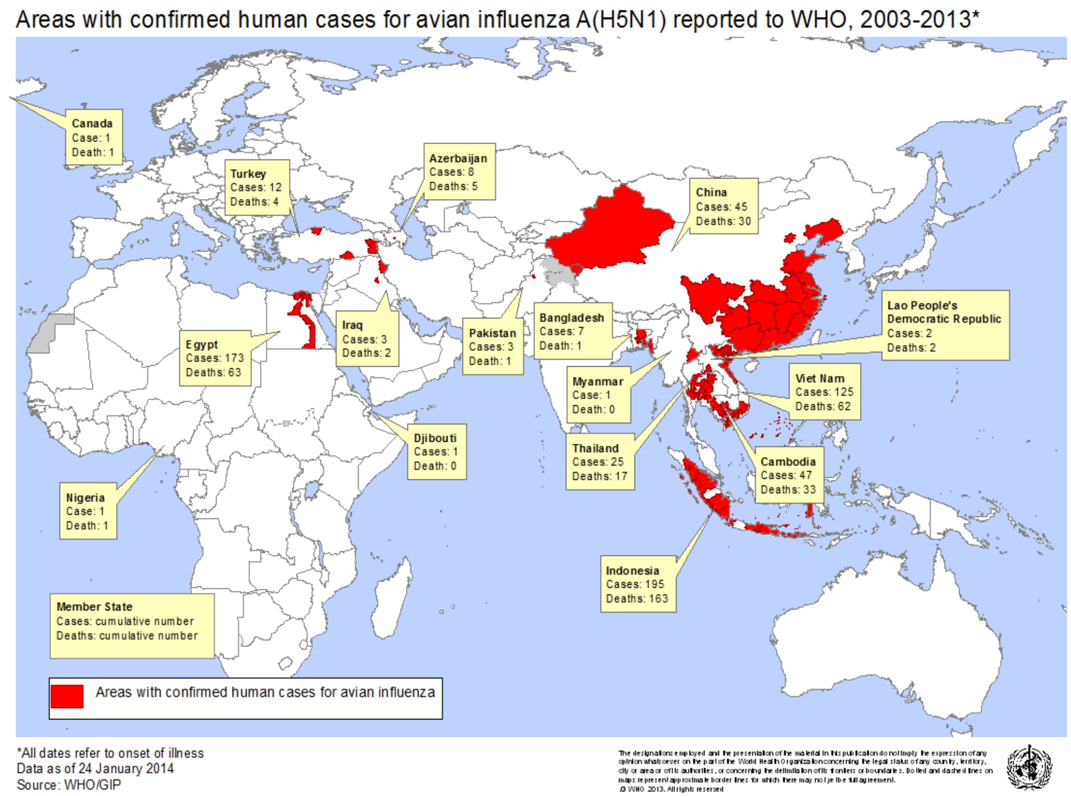
http://www.cdc.gov/flu/pdf/swineflu/prevent-spread-flu-pigs-at-fairs.pdf

H5N1 Avian Influenza

- First human cases identified in 1997
  - Hong Kong
  - 18 cases, 6 deaths
- Reemergence, 2003–present
  - Continued sporadic cases
  - Peaks in colder months
  - Limited person-to-person spread

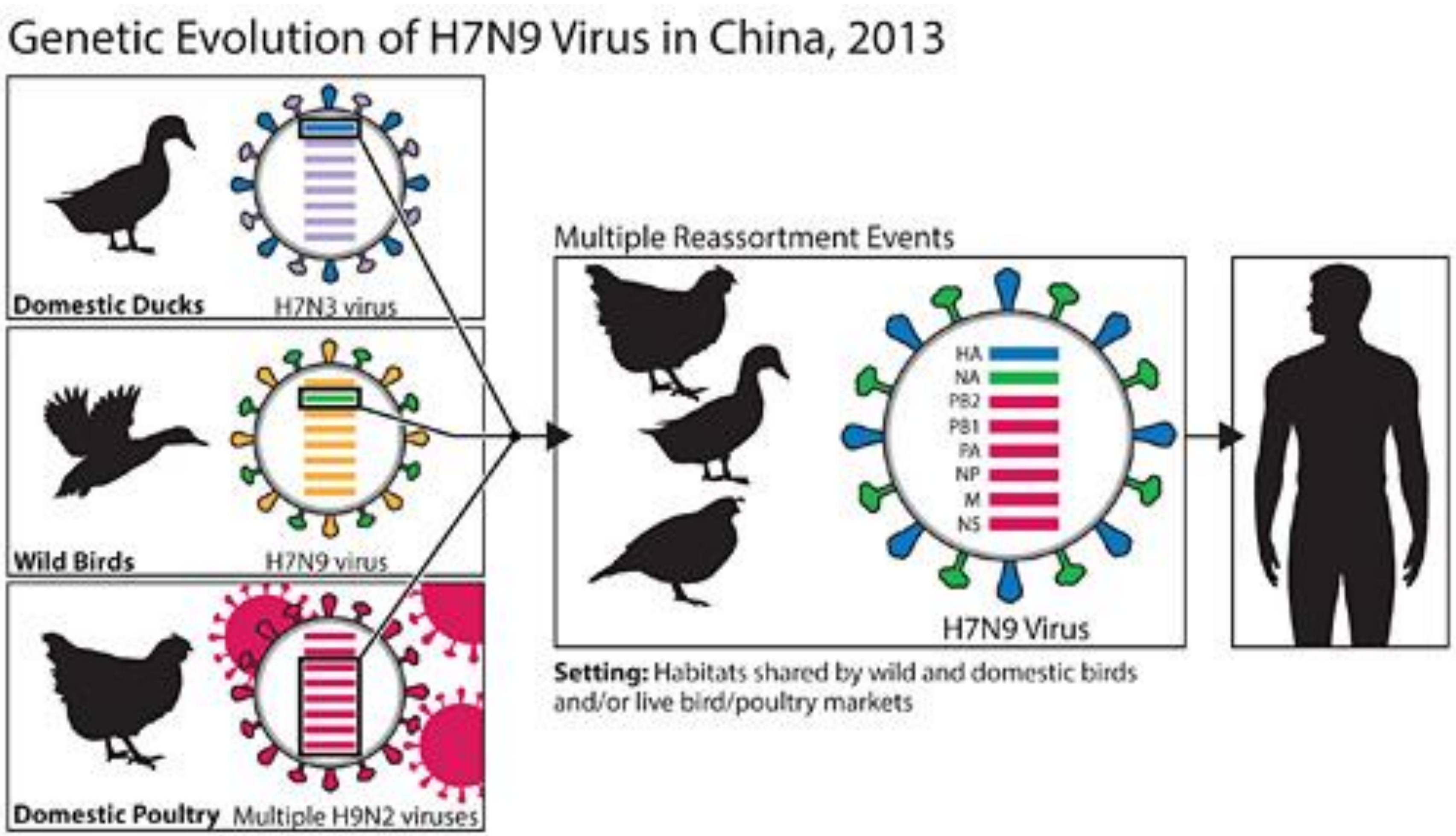
H5N1: WHO Update, November 15, 2015

- 884 cases
- 449 deaths (51%)
- 16 countries
- Progression from Asia to Middle East, North Africa



http://gamapserver.who.int/mapLibrary/Files/Maps/2003_AvianInfluenza_GlobalMap_01Feb13.png

H7N9 Avian Influenza



H7N9

- First human infection with avian H7N9 virus detected March, 2013
- 681 cases, 275 deaths (November 13, 2015)
  - Most with severe respiratory illness
- No sustained person-to-person transmission
- (Yet)

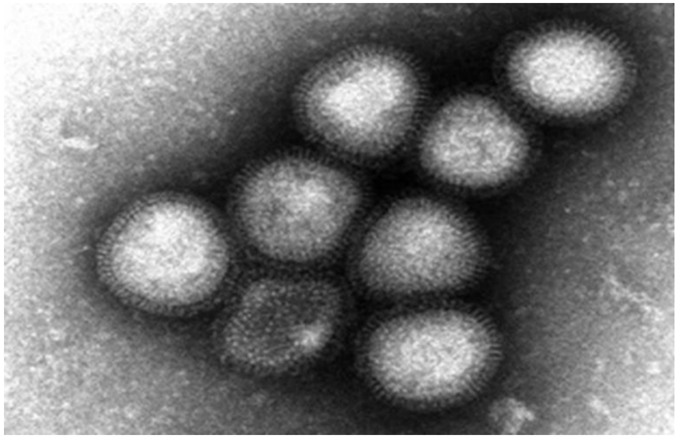


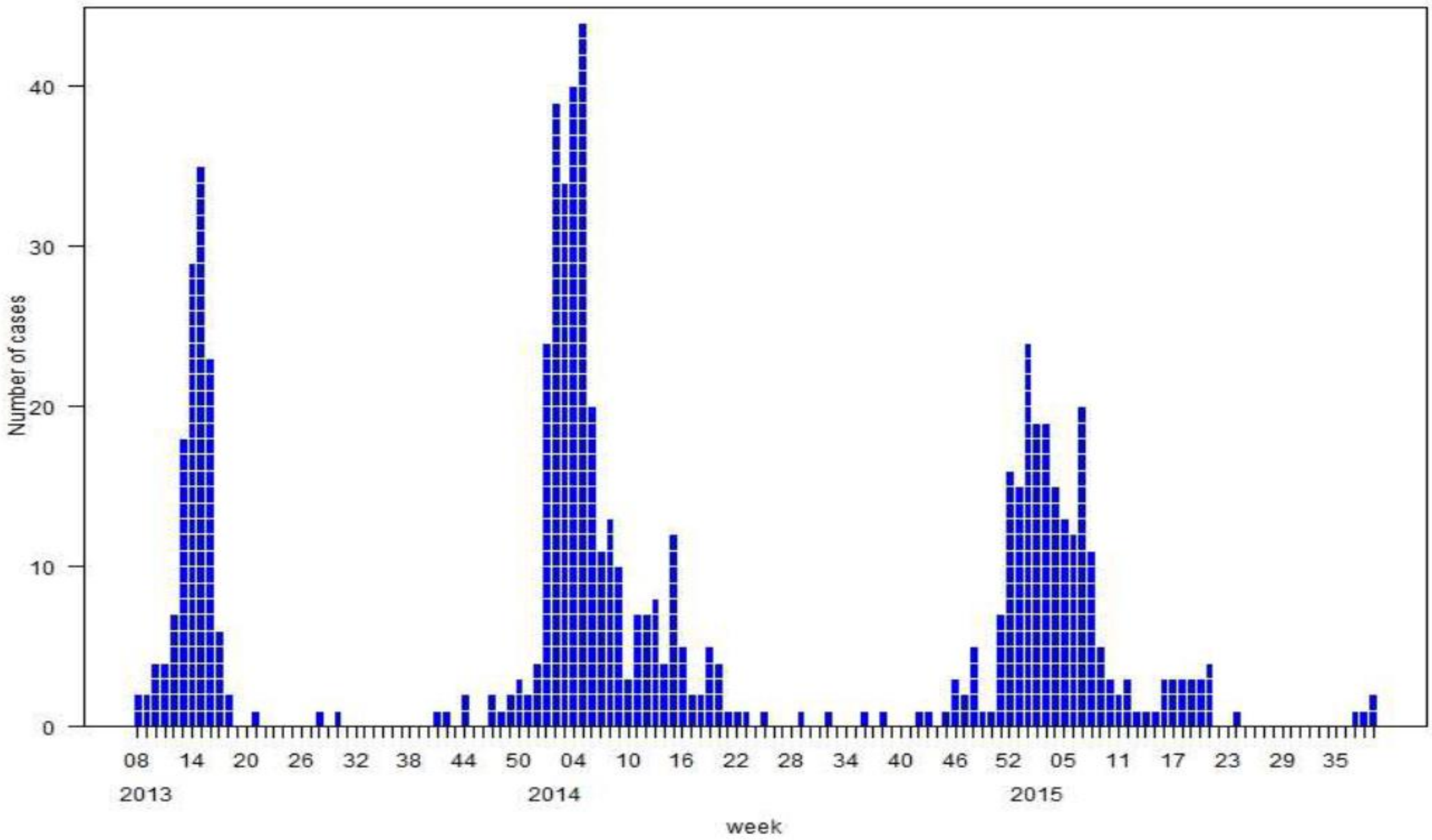
Image: H7N9 virus, National Institute of Infectious Diseases, Japan

H7N9

- All cases exposed in Eastern China
  - Cases identified in travelers to Malaysia, Canada
- Most had contact with poultry/markets

H7N9 – Seasonal Pattern?

Figure 1: Epidemiological curve of avian influenza A(H7N9) cases in humans by week of onset.



H7N9: The Bad News

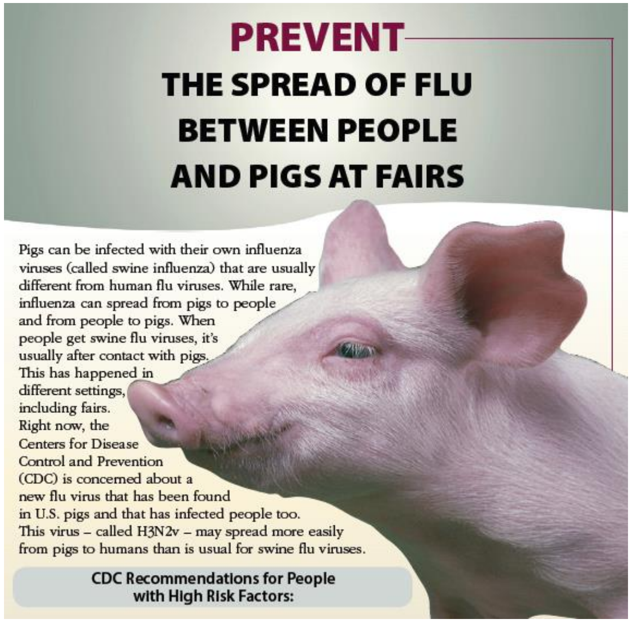
- Birds don’t show symptoms
  - Different from H5N1
  - Challenge for identification and control efforts
- Virus adapted to spread easily to mammals
- Very severe illness; 40% case-fatality

H3N2 variant (H3N2v)

- “Variant”: Virus that normally infects pigs
- **2010:** Swine H3N2 with matrix (M) gene from H1N1 virus identified in US pigs
- **2011:** 12 human cases of H3N2v infection detected in IN, IA, ME, PA, and WV
- **2012:** 309 cases in 12 states (245 in IN, OH)
- **2013:** 19 cases in 5 states (14 in IN)

H3N2v

- Illness similar to seasonal influenza
- Majority of cases were among children
- Most associated with prolonged exposure to pigs at agricultural fairs



Images: www.cdc.gov/flu

H3N2v: What’s Next?

- Only 3 human cases reported in 2014
  - Ohio and Wisconsin
  - No sustained spread
- 2 cases so far in 2015
  - Michigan and Minnesota
- Widely detected in pigs
- Sporadic cases and localized outbreaks could continue

H3N2v: Public Guidance

- Anyone at high risk for serious flu complications should avoid pigs and swine barns
- Stay away from sick pigs
- Wash your hands with soap and running water before and after exposure to pigs

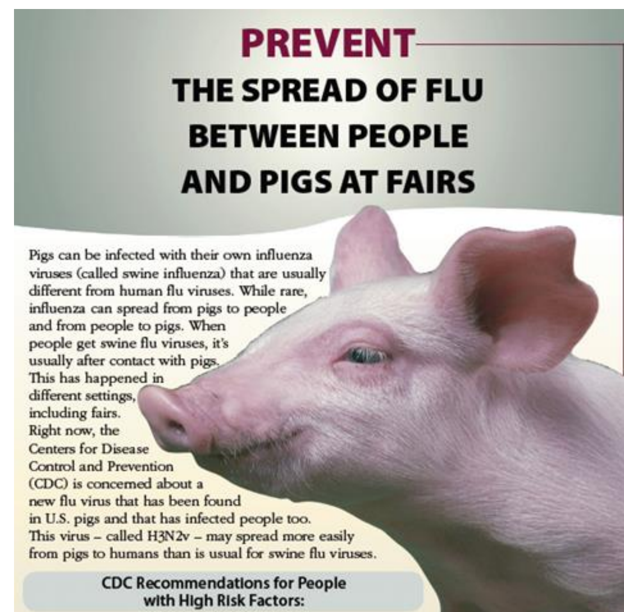


Image: www.cdc.gov/flu

Transmission

How Flu Spreads

- Spread through coughing and sneezing
- Contact transmission also important
  - Hand to hand, contaminated surfaces
- Airborne transmission possible

Survival of Influenza Outside the Body

- Plastic and stainless steel
  - Recoverable for >24 hours
  - Transferable to hand for up to 24 hours
- Cloth, tissue
  - Recoverable for 8–12 hours
  - Transferable to hands for ~15 minutes
- Hands
  - <5 minutes at high viral titers

Bean et al, JID 1982;146:47-51

Treatment

Influenza Antiviral Medications

- Adamantanes (M2 inhibitors)
  - Amantidine and rimantidine
  - Active against influenza A only
  - Not effective against currently circulating strains
- Neuraminidase Inhibitors (NAIs)
  - Oseltamivir, zanamivir, peramivir IV
  - Active against influenza A and B

Neuraminidase Inhibitors: Mechanism of Action

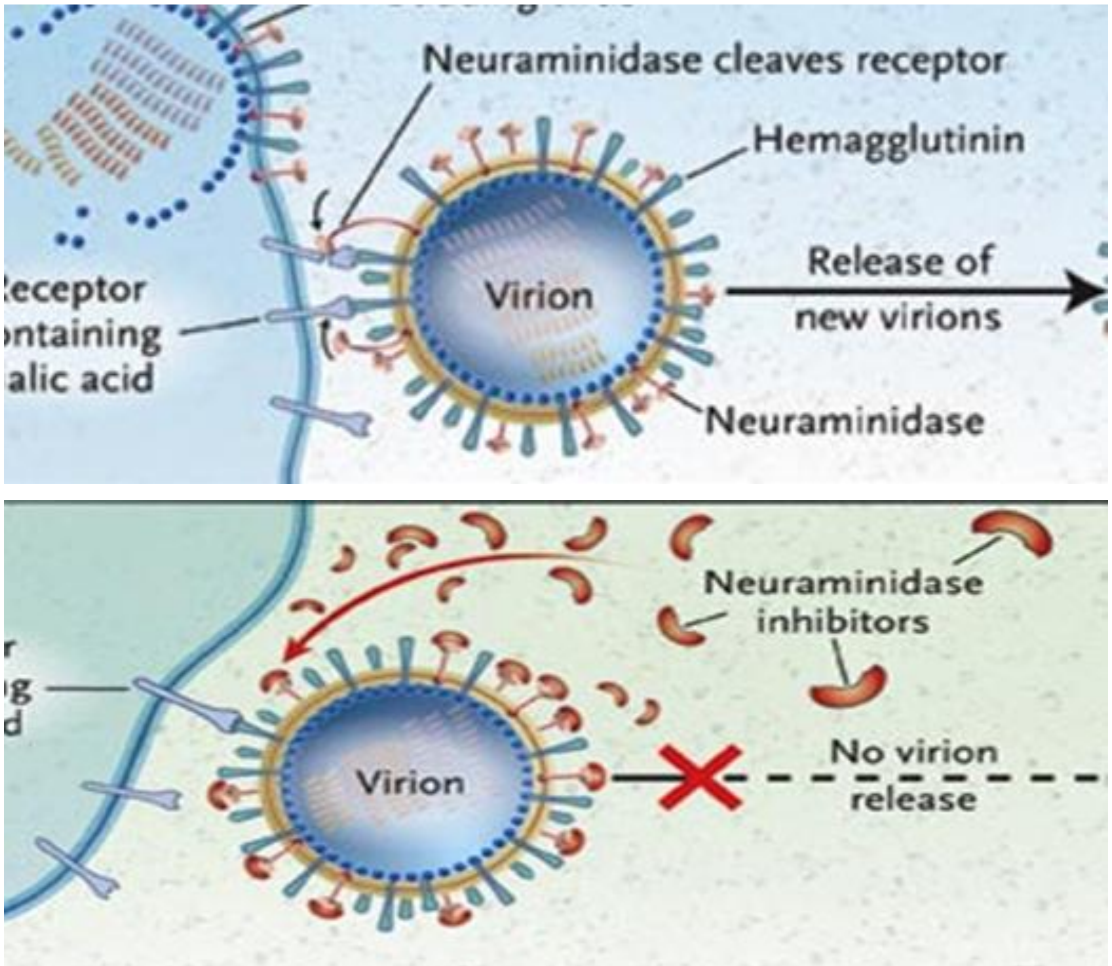


Image: Moscona A, New Engl J Med 2005. 353:1363-1373

- NA enables viral release from infected cells and replication
- NAIs block virus release from infected cells

Antiviral Effectiveness

Uncomplicated illness:

- NAIs reduce duration of illness by ~1 day if started <48 hours after onset
- Effect may be greater in children 1–3 years*

Severe illness:

- Oseltamivir associated with decreased mortality among hospitalized patients
- Benefit <u>even if treatment delayed</u>

*Heinonen et al. Clin Infect Dis 2010

Antiviral Resistance

- Develops in flu A more often than flu B
- Sporadic cases frequently identified in
  - Immunocompromised patients
  - Patients who received oseltamivir prophylaxis
- Local transmission/clusters described
- Potential for rapid spread

CDC
MMWR
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr
Weekly September 11, 2009 / Vol. 58 / No. 35

Oseltamivir-Resistant 2009 Pandemic Influenza A (H1N1) Virus Infection in Two Summer Campers Receiving Prophylaxis — North Carolina, 2009

Initial testing of the 2009 pandemic influenza A (H1N1) virus found it susceptible to neuraminidase inhibitors (oseltamivir and zanamivir) and resistant to adamantanes (amantadine and rimantadine) (*1*). Neuraminidase inhibitors have been used widely for treatment and chemoprophylaxis of 2009 pandemic influenza A (H1N1); however, sporadic cases of oseltamivir-resistant 2009 pandemic influenza A (H1N1) virus infection have been reported worldwide (*2*), including nine U.S. cases identified as of September 4.* On July 14, CDC was contacted by a physician at a summer camp in North Carolina regarding two cases of influenza-like illness (ILI) in

MAJOR ARTICLE

Cluster of Oseltamivir-Resistant 2009 Pandemic Influenza A (H1N1) Virus Infections on a Hospital Ward among Immunocompromised Patients—North Carolina, 2009

Luke F. Chen,[1,2] Natalie J. M. Dailey,[4,5] Agam K. Rao,[5,6] Aaron T. Fleischauer,[4,7] Ian Greenwald,[3] Varough M. Deyde,[8] Zack S. Moore,[4] Deverick J. Anderson,[1,2] Jonathan Duffy,[5,6] Larisa V. Gubareva,[8] Daniel J. Sexton,[1,2] Alicia M. Fry,[8] Arjun Srinivasan,[6] and Cameron R. Wolfe[2,3]

[1]Program for Infection Prevention and Healthcare Epidemiology, [2]Division of Infectious Diseases, and [3]Duke Preparedness and Response Center, Duke University Medical Center, Durham, North Carolina; [4]North Carolina Department of Health and Human Services, Raleigh, North Carolina; and [5]Epidemic Intelligence Service, [6]Division of Healthcare Quality Promotion, [7]Career Epidemiology Field Officer Program, and [8]Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia

Background. Oseltamivir resistance among 2009 pandemic influenza A (H1N1) viruses (pH1N1) is rare. We investigated a cluster of oseltamivir-resistant pH1N1 infections in a hospital ward.

Methods. We reviewed patient records and infection control measures and interviewed health care personnel (HCP) and visitors. Oseltamivir-resistant pH1N1 infections were found with real-time reverse-transcription polymerase chain reaction and pyrosequencing for the H275Y neuraminidase (NA) mutation. We compared hemagglutinin (HA) sequences from clinical samples from the outbreak with those of other surveillance viruses.

Results. During the period 6–11 October 2009, 4 immunocompromised patients within a hematology-

“Mutated Flu Virus in NC”

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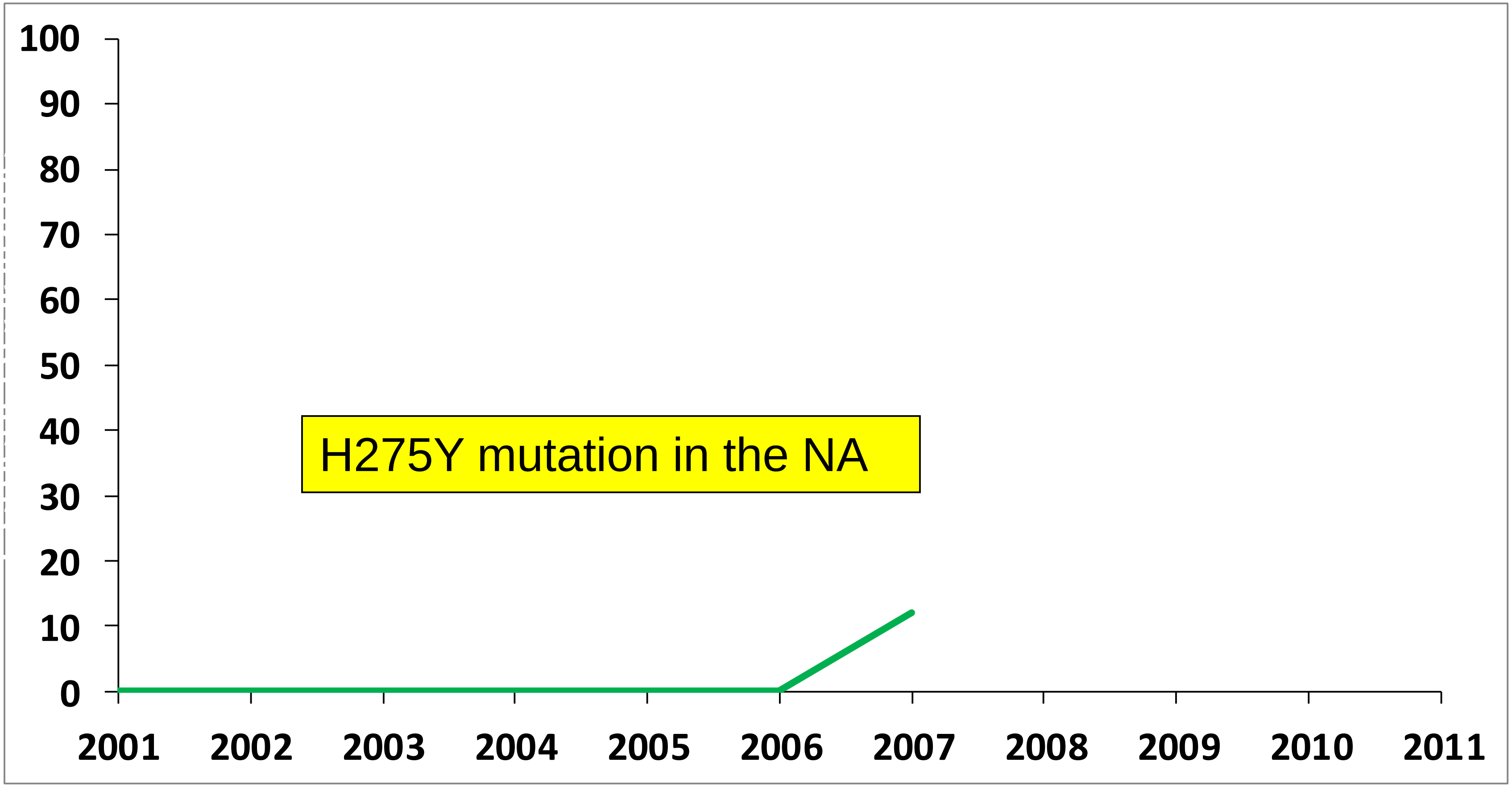
RALEIGH, N.C. — State and federal public health officials are examining a cluster of influenza B viruses found only in North Carolina that appear to be less responsive to a common antiviral drug than typical flu viruses.

A genetic change in the viruses not seen in samples from other states makes them harder to treat with Tamiflu, officials said Monday.

"These particular viruses are less sensitive to the drug in the lab, but they are not resistant," Dr. Zack Moore of the state Division of Public Health said in a statement. "We want to

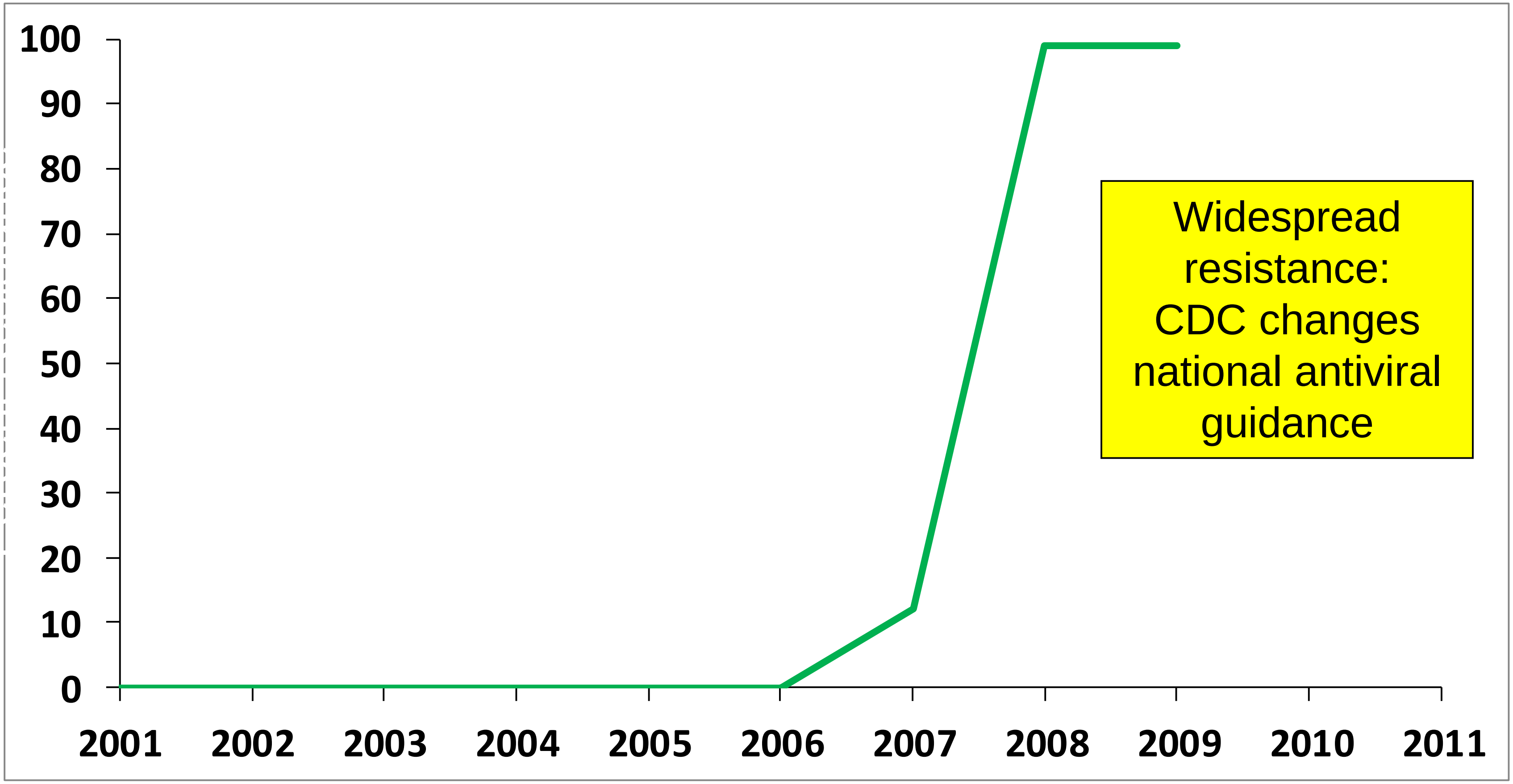
RELATED
Mutated flu strains appear in NC

Emergence of Oseltamivir Resistance in Seasonal Influenza A H1N1, 2007–2009



Sheu. Antimicrob Agents Chemo; 2008. MMWR. 2009:58;115-119

Emergence of Oseltamivir Resistance in Seasonal Influenza A H1N1, 2007–2009



Sheu. Antimicrob Agents Chemo; 2008. MMWR. 2009:58;115-119

Prevention

Flu Vaccine: Lots of Choices

- Standard dose or high dose
- Intramuscular, intranasal or intradermal
- Egg culture, cell culture or recombinant
- Trivalent or quadrivalent

Okay- but does it work?

- Short answer: Yes
- Long answer: During 2014-15 influenza season, flu vaccine reduced the risk of having to seek medical care for flu by 23%
- Longer answer:
  – 13% effective against A(H3N2)
  – 55-63% effective against influenza B viruses

http://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm

Flu Vaccine Effectiveness Estimates, 2005–2015

Influenza Season	No. of Patients	Adjusted VE	95% CI
2004-05	762	10	-36, 40
2005-06	346	21	-52, 59
2006-07	871	52	22, 70
2007-08	1914	37	22, 49
2008-09	6757	56	23, 75
2009-10	4757	60	53, 66
2011-12	4771	47	36, 56
2012-13	6452	49	43, 55
2013-14	5990	51	43, 58
2014-15	4913	23	7, 49

http://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm

Flu Vaccine Take Home

- The most effective tool for prevention
- Usually reduce the risk of having to seek medical care for influenza by about half
  - Varies by age group, flu strain, other factors
- Prevent complications, hospitalizations and deaths due to influenza
  - Estimated 40,000 deaths averted August 2005–June 2014

Foppa et al. doi:10.1016/j.vaccine.2015.02.042

Influenza Epidemiology

Seasonal Flu: The Big Picture

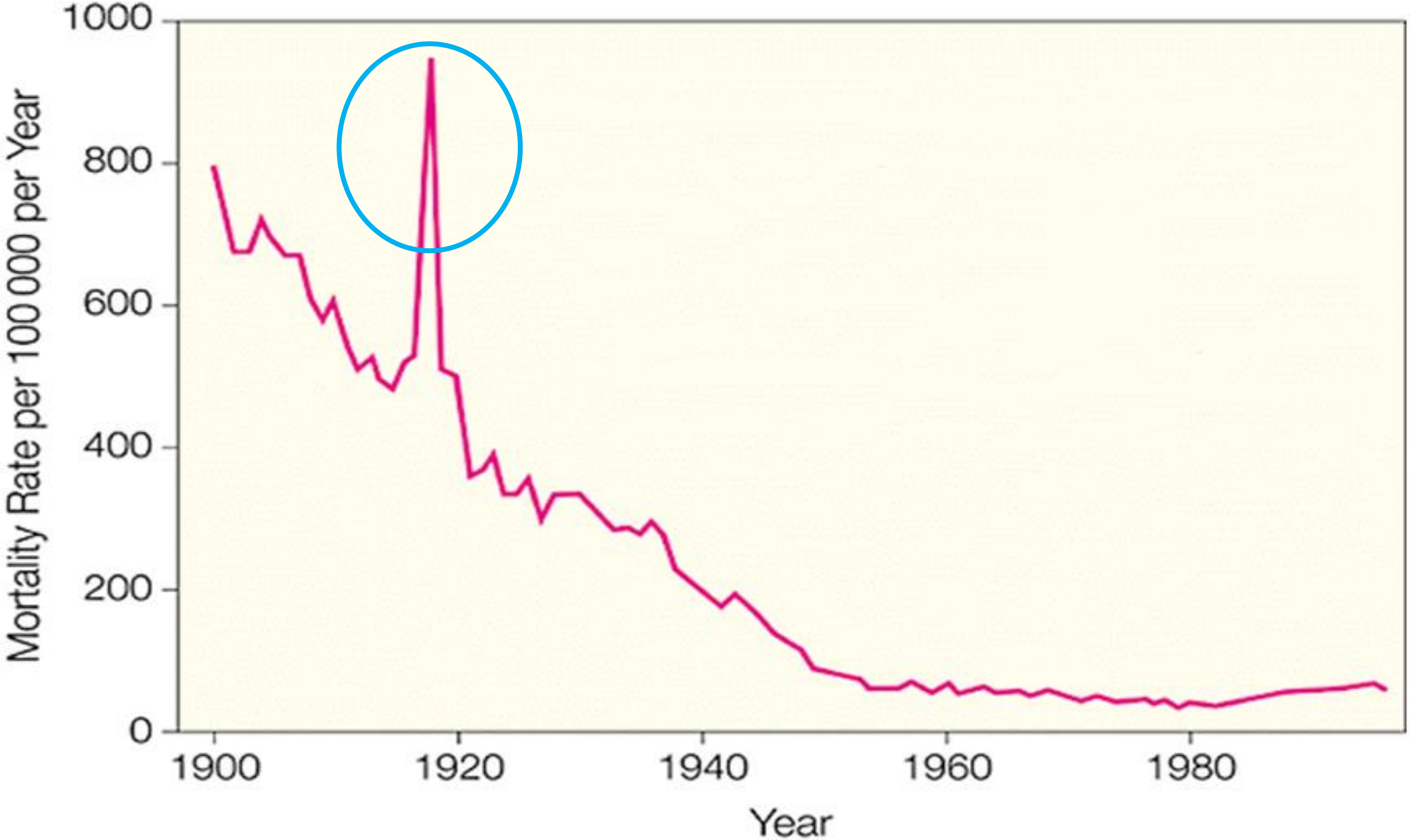
- Affects 5–20% of the population each year
  - >200,000 hospitalizations*
  - Average 24,000 deaths (range, 3–49,000)**
- $10 billion direct medical costs
- $87 billion total economic burden***

Thompson, JAMA 2004; **MMWR 59(33) 2010; ***Molinari, Vaccine 2007

Impact of Influenza Pandemics

Pandemic, or Antigenic Shift	Excess Deaths in US	Populations Affected
1918-19 (A/H1N1)	500,000	Persons <65 years
1957-58 (A/H2N2)	70,000	Infants, elderly
1968-69 (A/H3N2)	36,000	Infants, elderly
2009-10 (A/H1N1)	12,500	Persons <65 years

Infectious Disease Mortality in the US, 1900–1996

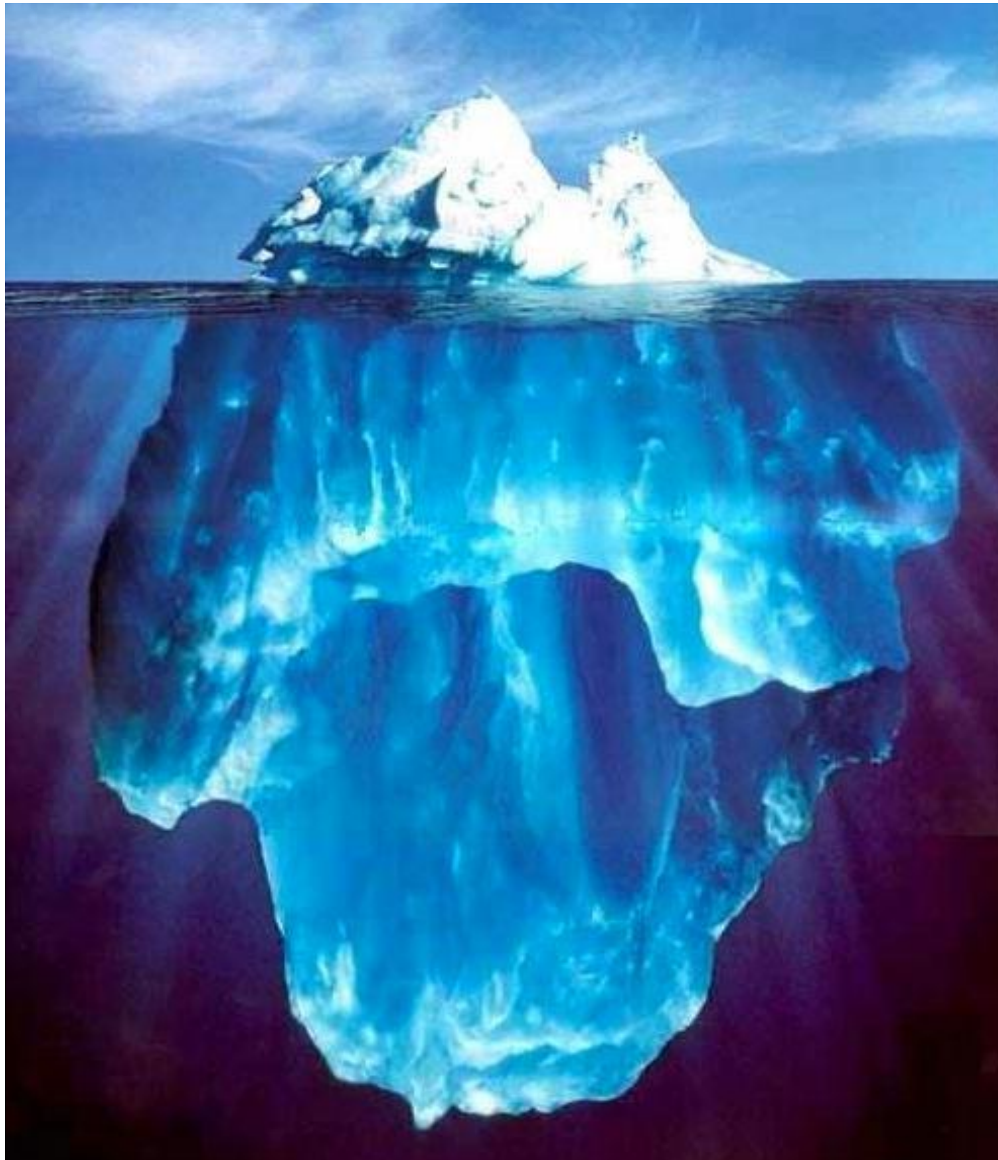


Armstrong, et al. *JAMA* 1999;281:61-66. Adapted from CDC slide set

Flu Surveillance: A “Special Case”

- Cases are not individually notifiable despite
  - High incidence/ highly transmissible
  - High morbidity and mortality
  - Effective public health interventions
  - Pandemic potential
- Need for coordinated state, national, and international surveillance

Influenza Surveillance



Hospitalization

Outpatient

Not medically attended

Subclinical

Flu Surveillance Goals

1. Monitor onset, duration and spread
2. Detect changes in severity
   - Identify severely affected populations
3. Identify and track mutations
   - Novel strains, match to vaccine, antiviral resistance

- ➢ Guide interventions
- ➢ Provide information to partners

Influenza Surveillance

Relies on:

1. Tracking influenza-like illness
2. Systematic laboratory testing
3. Monitoring disease severity

Influenza Surveillance: Data Sources

A. Influenza-like Illness Network (ILINet)*
B. NC Disease Event Tracking and Epidemiologic Collection Tool (NC DETECT) / Public Health Epidemiologist Network
C. Case based reporting
   - Flu associated deaths*
   - Novel Influenza*

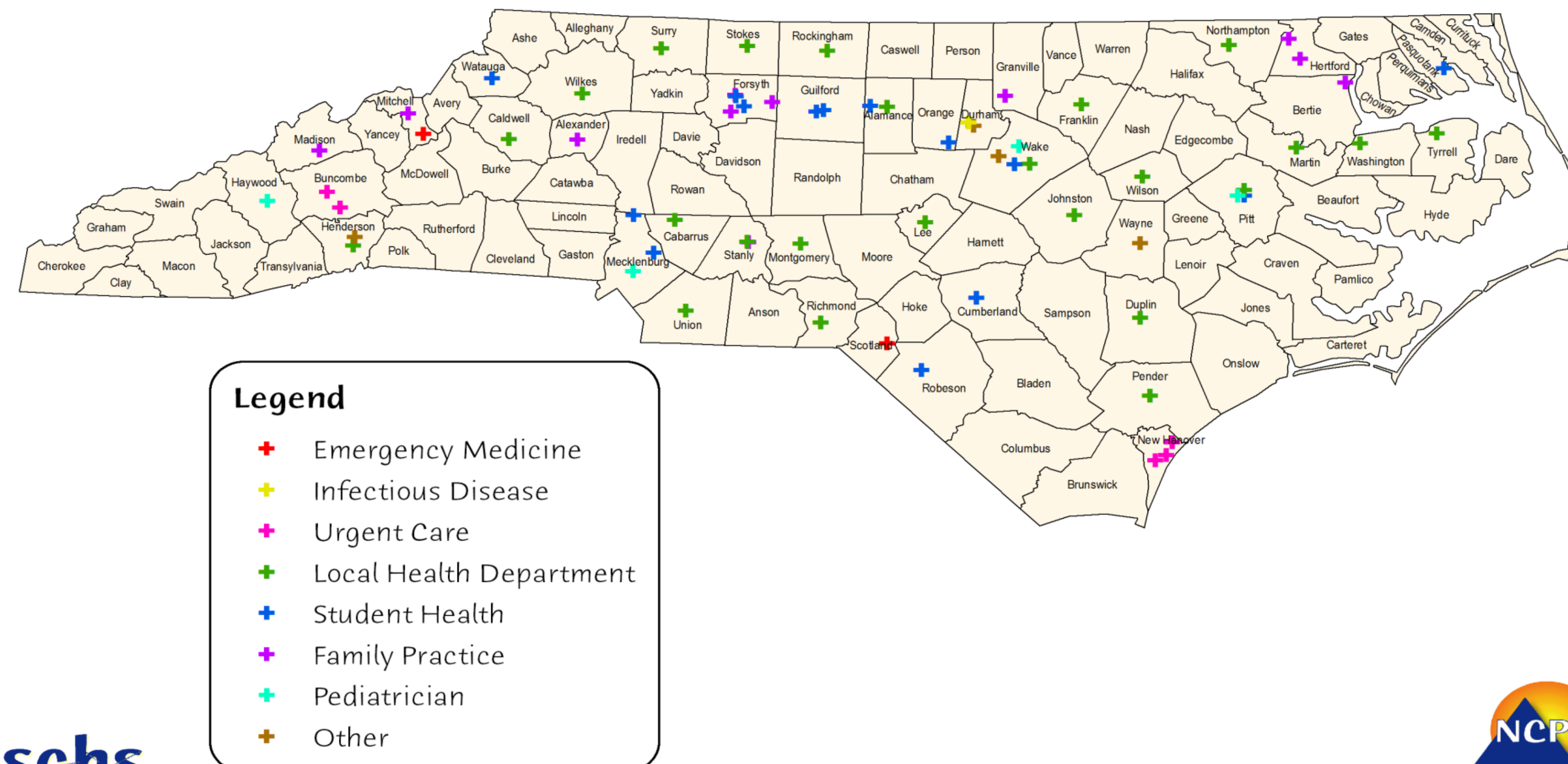
*Include laboratory component

Influenza-like Illness Network (ILINet)

- Background on ILINet: A voluntary network of providers based on population size that electronically report influenza-like illness to CDC.
- Provide weekly updates on the number of patients seen with ILI and send specimens to the state lab of public health
  - Serve as an important source for lab surveillance
- 68 sites enrolled for the 2015-16 season
  - 21 Health Departments
  - 19 Private medical offices
  - 14 student health centers
  - 14 Other sites (hospitals, urgent cares, etc.)

Map of ILINet Providers in NC

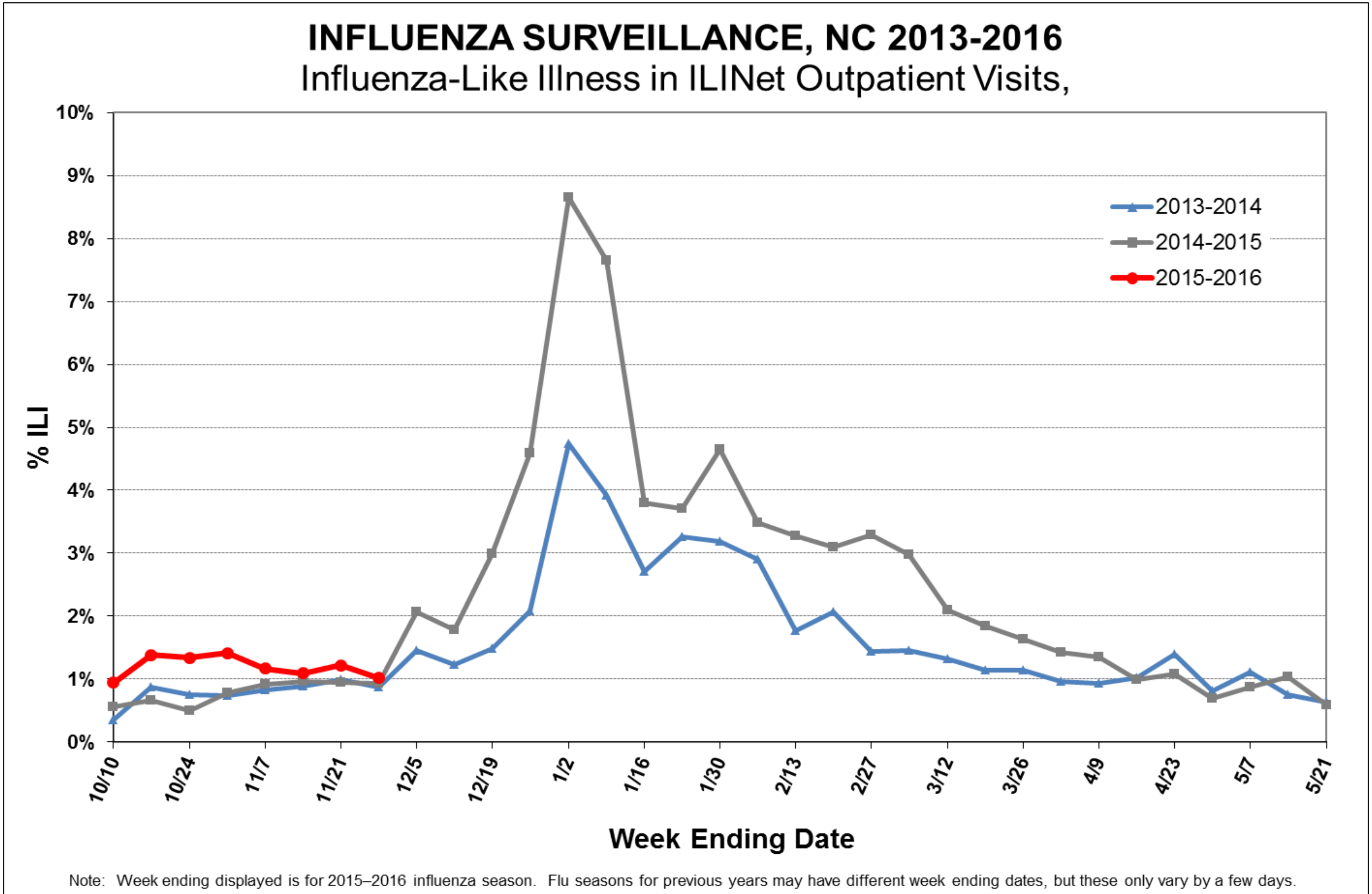
North Carolina ILI Network Provider Locations 2015-2016



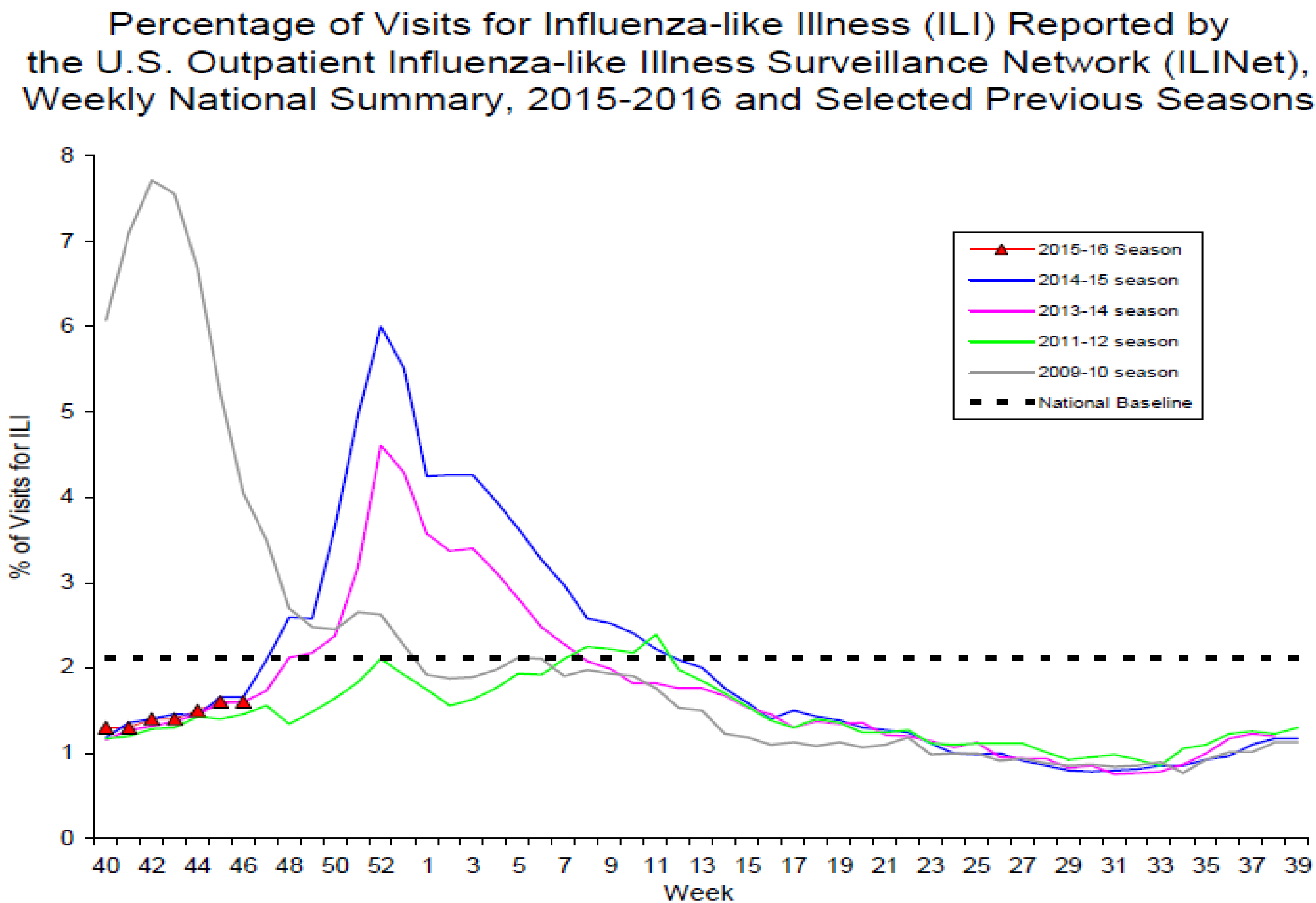
sehs State Center for Health Statistics

NCPH North Carolina Public Health

ILINet Data: North Carolina



ILINet Data: National

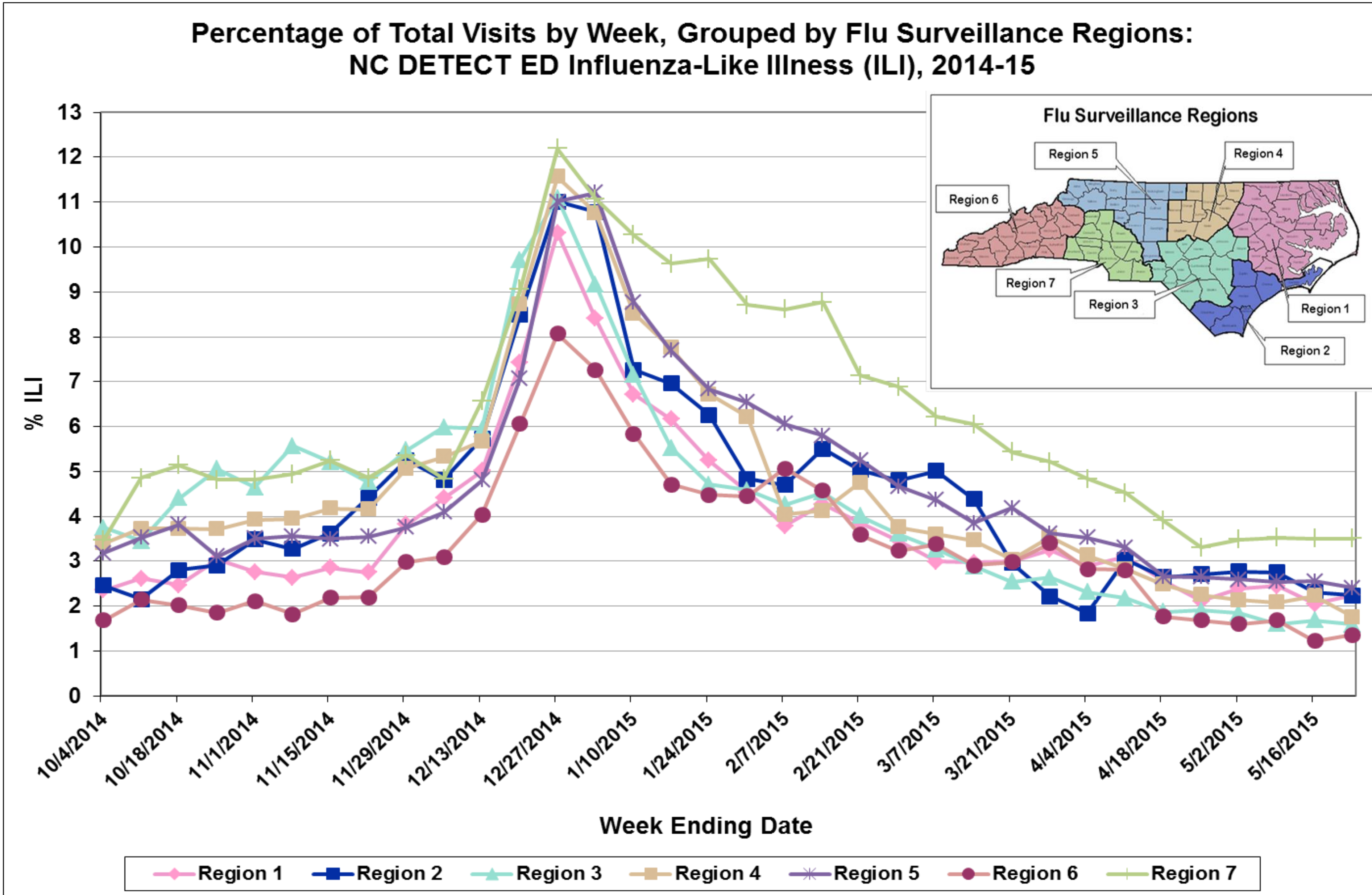


NC DETECT

- Electronic surveillance of all emergency department visits statewide

- Tracks visits/admissions for flu-like illness
  - Can separate by region (patient zip code)
  - Includes disposition (admitted vs. discharge); helps monitor changes in severity

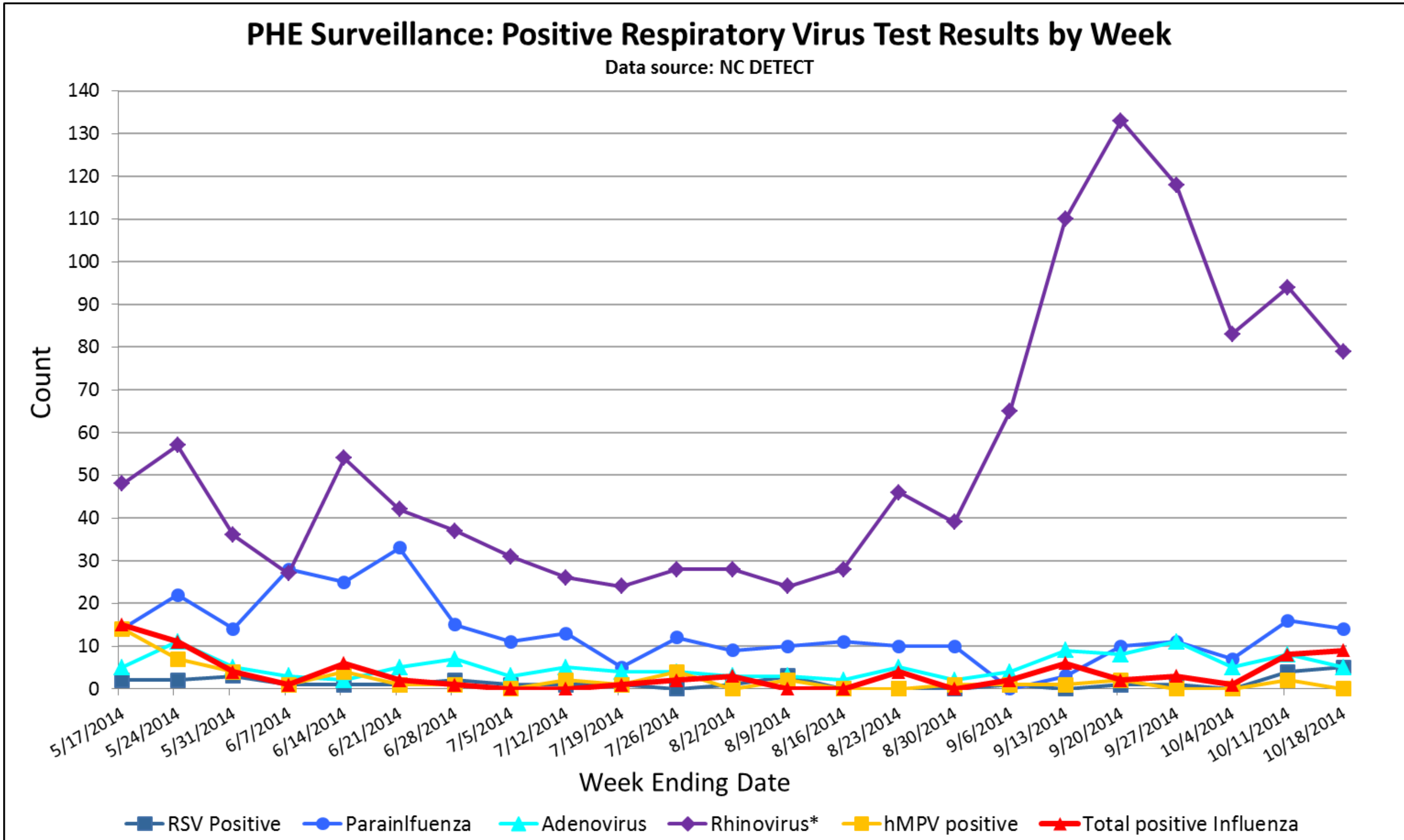
NC DETECT Data



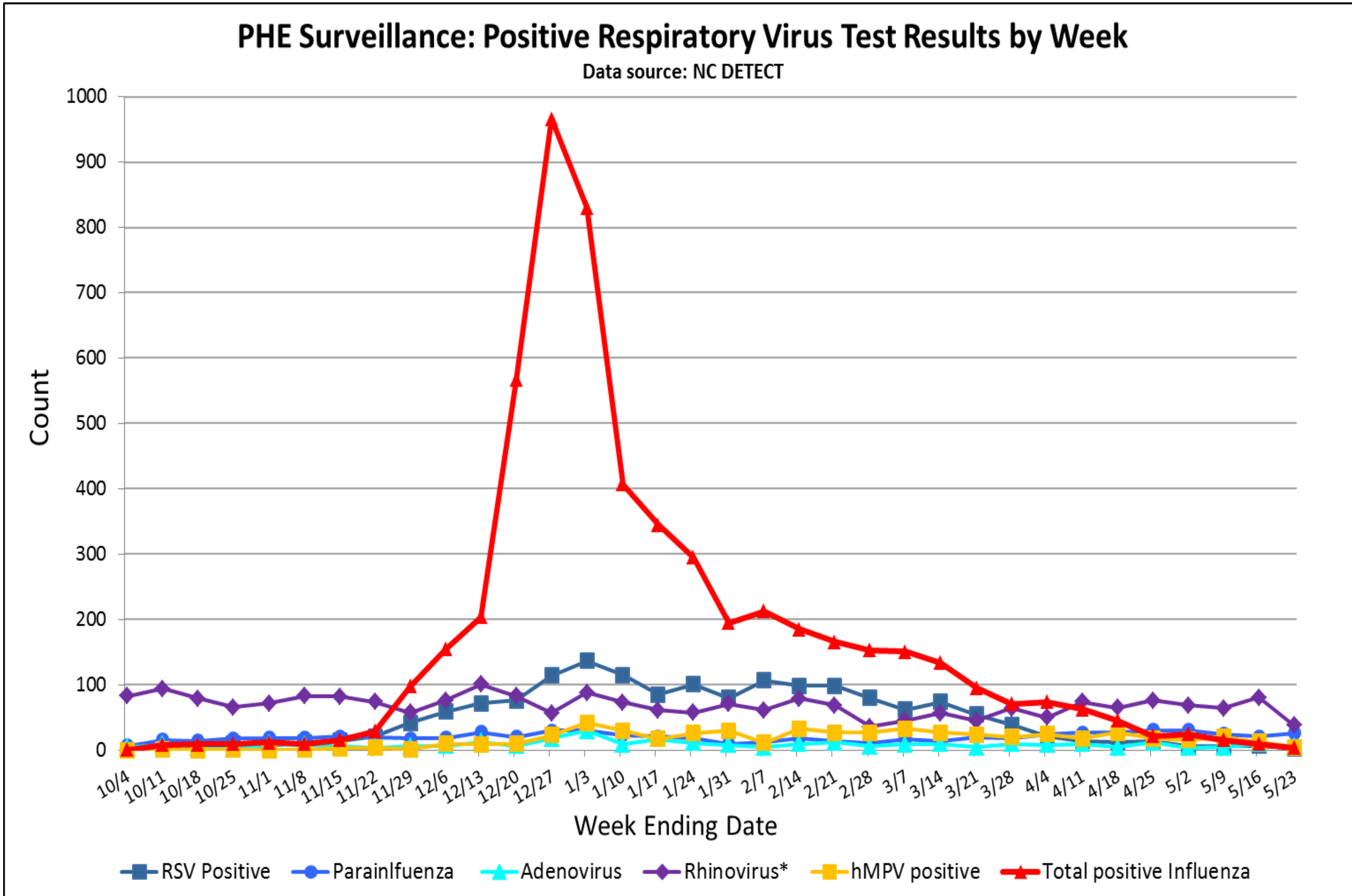
Hospital Based Public Health Epidemiologist Network

- 7 Public Health Epidemiologists located at seven major hospital systems in NC
- Report the number of flu positives seen in their facilities along with other respiratory illnesses each week-
  - Flu positives
  - Positive respiratory illnesses
  - Hospital admissions by age group

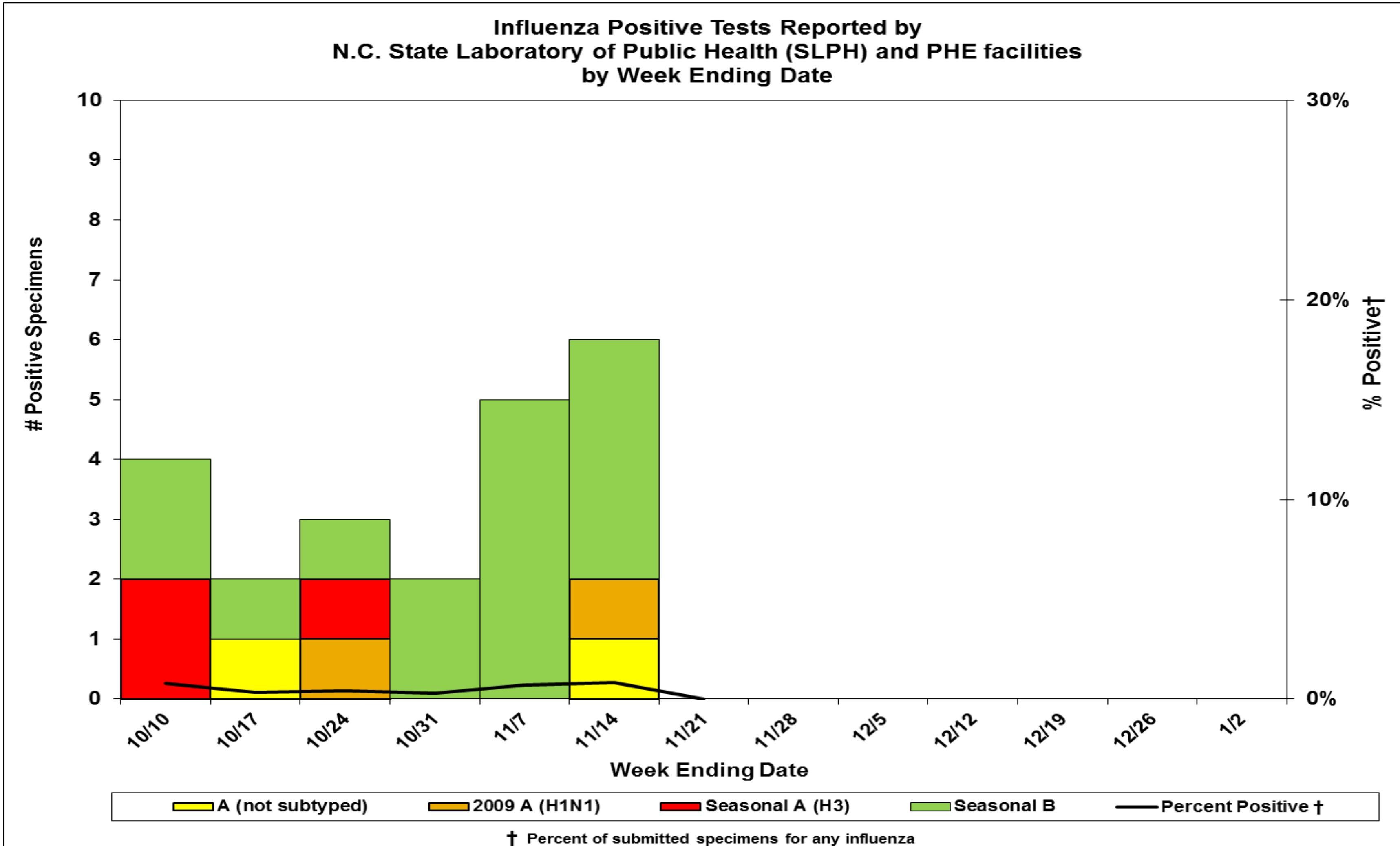
Public Health Epidemiologist Network: Respiratory Virus Test Results 2014-15



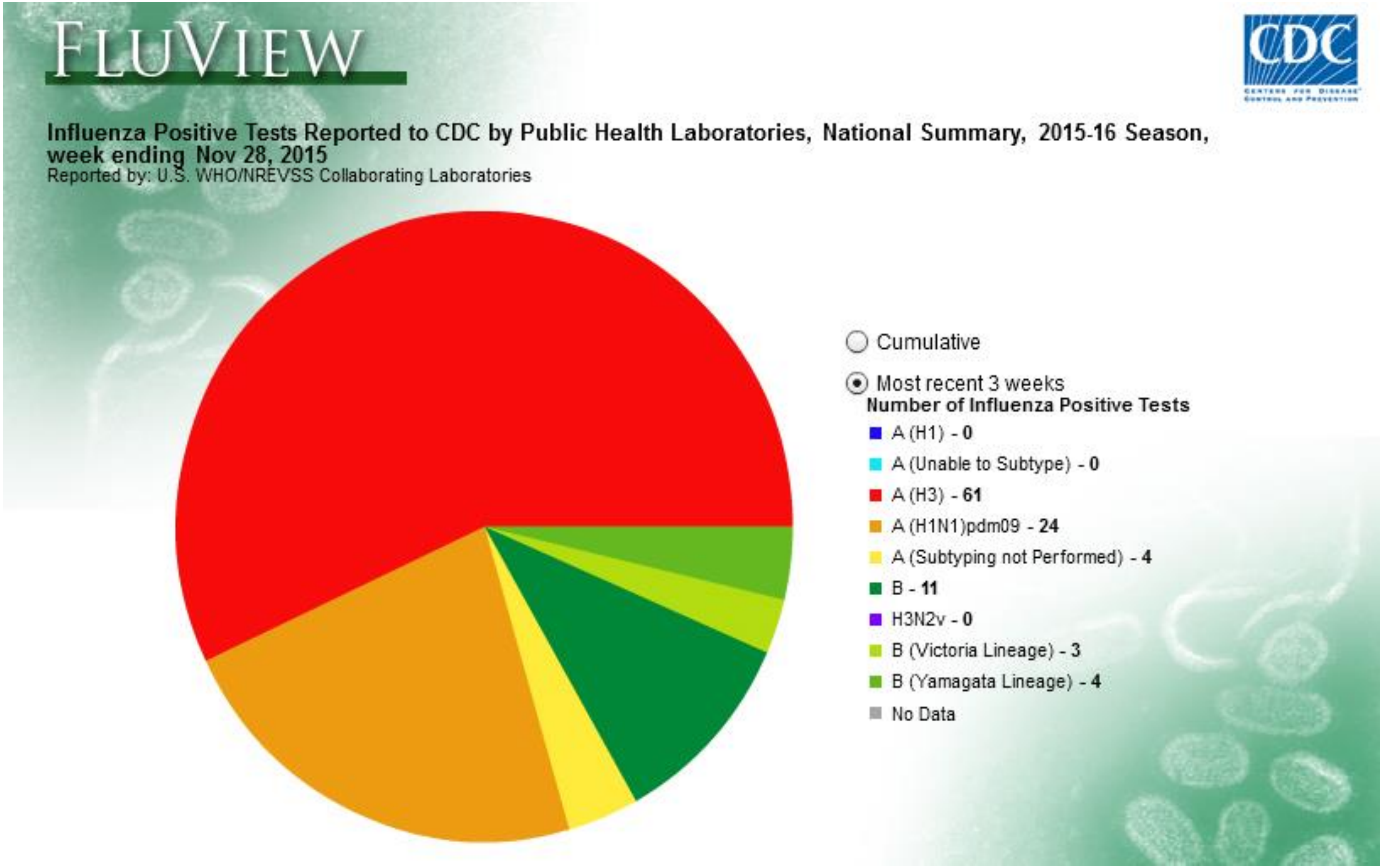
Public Health Epidemiologist Network: Respiratory Virus Test Results 2014-15



Virologic Testing Results: North Carolina, 2015-2016



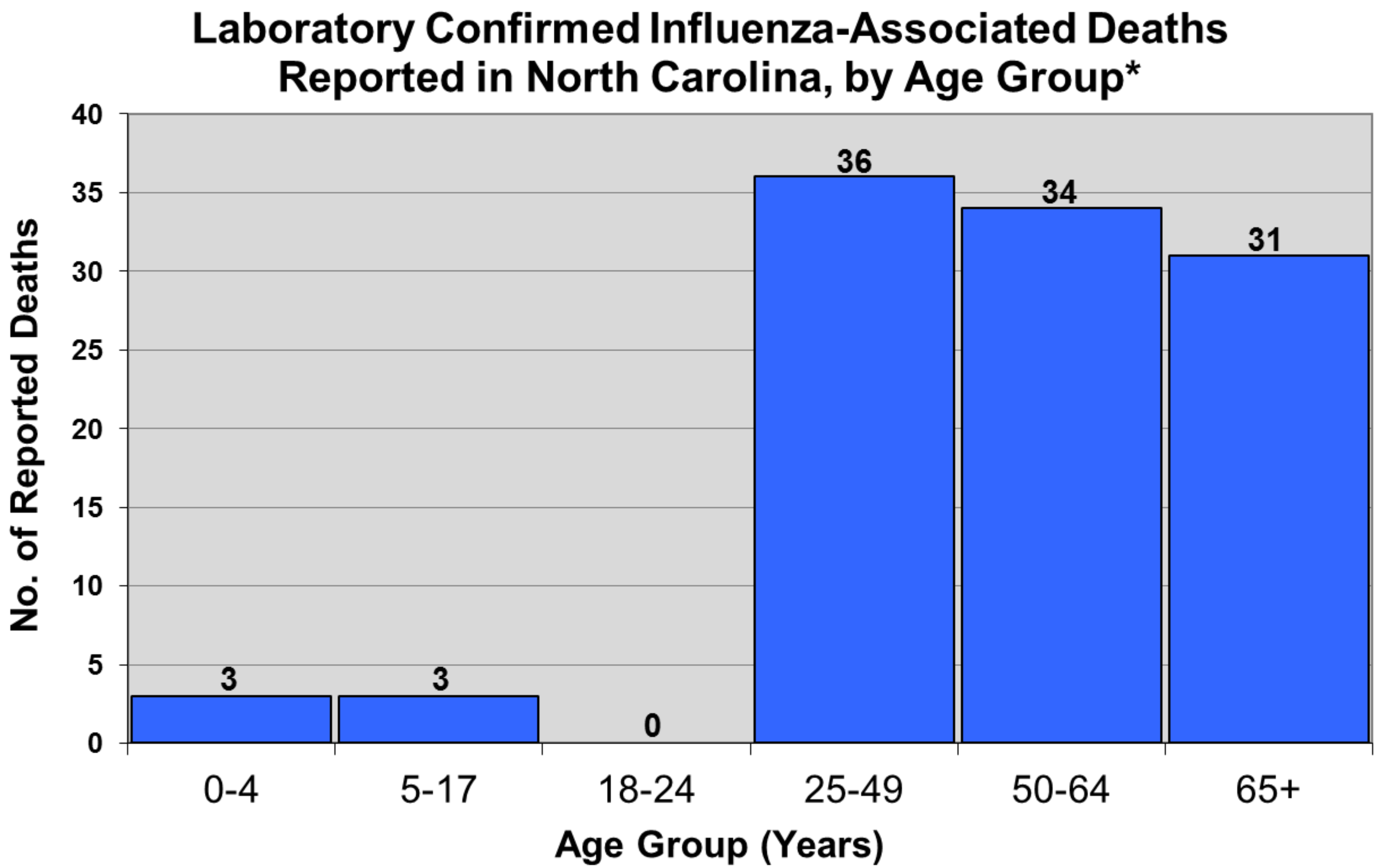
Virologic Testing Results: National



Flu Associated Deaths

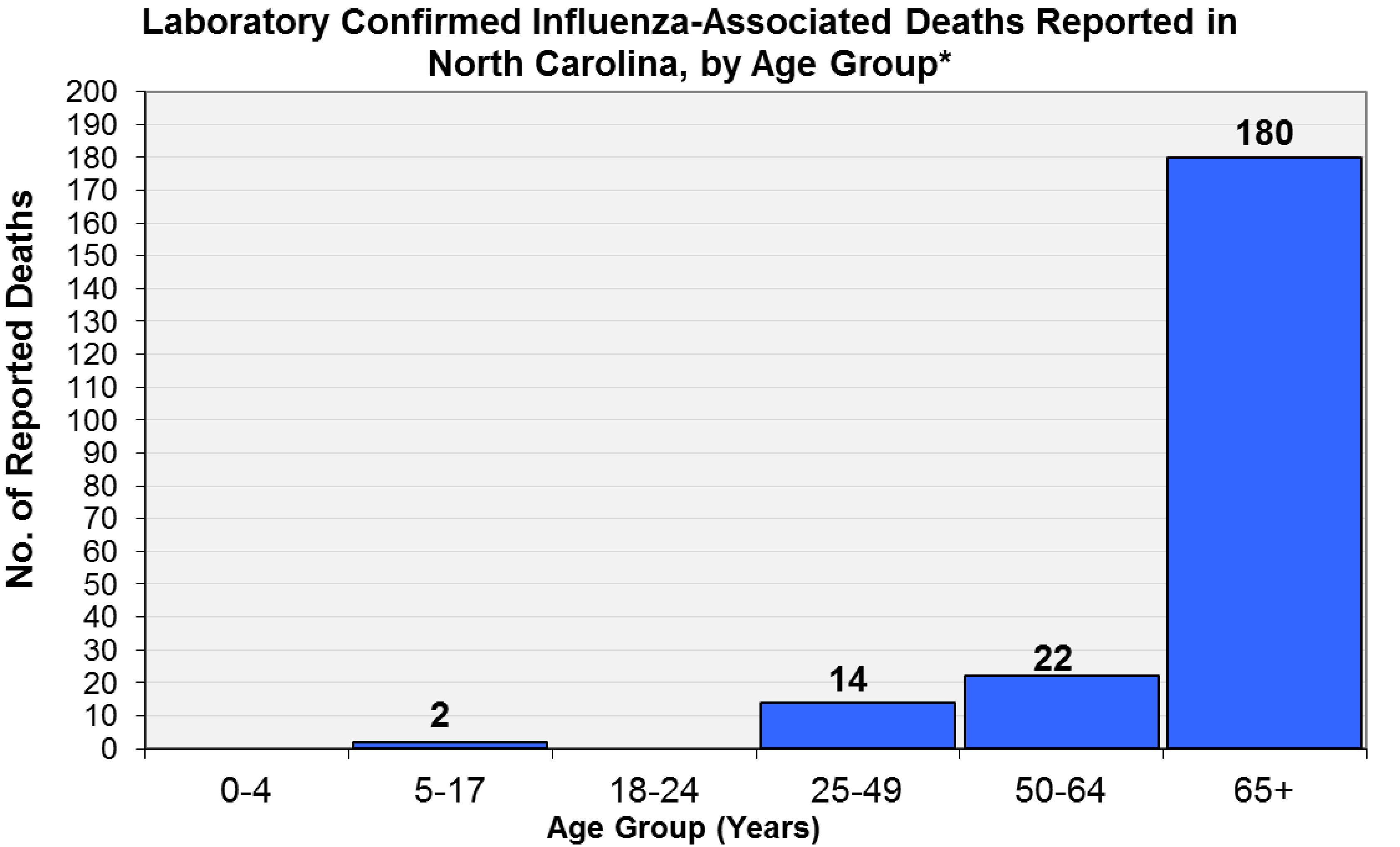
- Pediatric influenza-associated deaths made reportable in 2004 (nationally notifiable)
- Adult influenza-associated deaths made reportable in NC beginning October 1, 2009
- "…clinically compatible illness confirmed by an appropriate laboratory or rapid diagnostic test"

Flu Associated Death Data: 2013-14 (Pandemic H1N1 Predominant)



*An influenza-associated death is defined for surveillance purposes as a death resulting from a clinically compatible illness that was confirmed to be influenza by an

Flu Associated Death Data: 2014-15 (H3N2 Predominant)



*An influenza-associated death is defined for surveillance purposes as a death resulting from a clinically compatible illness that was confirmed to be influenza by an appropriate laboratory or rapid diagnostic test. The 2014-15 influenza season began on September28, 2014.

Conclusions

- Major cause of illness and deaths in humans
- Influenza surveillance in humans and animals is critical to help rapidly identify viruses with pandemic potential